Acute respiratory distress syndrome

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ABSTRACT

The understanding of acute respiratory distress syndrome (ARDS) has evolved greatly since it was first described in a 1967 case series, with several subsequent updates to the definition of the syndrome. Basic science advances and clinical trials have provided insight into the mechanisms of lung injury in ARDS and led to reduced mortality through comprehensive critical care interventions. This review summarizes the current understanding of the epidemiology, pathophysiology, and management of ARDS. Key highlights include a recommended new global definition of ARDS and updated guidelines for managing ARDS on a backbone of established interventions such as low tidal volume ventilation, prone positioning, and a conservative fluid strategy. Future priorities for investigation of ARDS are also highlighted.

Introduction

Acute respiratory distress syndrome (ARDS) is characterized by severe, diffuse inflammatory injury to the lung parenchyma resulting from a predisposing risk factor (for example, pulmonary or non-pulmonary infection, trauma, aspiration, or shock).[1] Before covid-19, ARDS was estimated to occur in approximately 10% of critically ill patients, with a high mortality rate of approximately 30-50%.[2] The covid-19 pandemic increased the incidence of ARDS,[3 4] although its exact impact on the incidence and outcomes of ARDS requires further study. Nevertheless, ARDS remains a highly fatal condition with long term sequelae.[5] Optimizing intensive care through appropriate ventilation and fluid management is still the most effective way to reduce the mortality and complications of ARDS.[6 7] In this article, we review the latest developments in ARDS, including the evolution of the definition of ARDS culminating in the most recent recommended revision to include patients receiving high flow nasal oxygen support.[8] We also present updates in the study of the epidemiology of and risk factors for ARDS and its pathophysiology, phenotyping, and management, as well as the current understanding of long term health consequences of ARDS and areas of future investigation. Where appropriate, we comment on the specific impact that the covid-19 pandemic has had on the current understanding of ARDS.

Sources and selection criteria

We identified references for this review through searches of publications listed by PubMed from its inception to 6 January 2024, except in the case of epidemiology, for which we restricted searches to after the 1994 publication of the American-European Consensus Conference (AECC) definition of ARDS. We used the search terms "ARDS"; "definition"; "epidemiology" with specific searches for "age", "race", and "sex"; "pathogenesis" with specific searches including "epithelial injury", "endothelial injury", "inflammation", "neutrophil", "platelet", and "cell-free hemoglobin"; "pathology"; "diffuse alveolar damage"; "management"; "ventilator"; "ECMO"; "statin"; "acetaminophen"; "beta agonist"; "corticosteroid"; "cell therapy"; "mesenchymal stromal cell"; and "extracellular vesicles". We also selected references from our personal libraries that were not identified by database searching. We screened relevant review articles for additional references. We considered in vitro, animal, and human studies, giving preference to human clinical studies and randomized controlled trials (RCTs) and meta-analyses when available. We reviewed only articles published in English. We excluded papers if they were not peer reviewed (including preprint articles), were from small or uncontrolled case series, or included duplicate data. If articles pertained to similar topics, we selected more recent articles. For some topics, we selected succinct review articles or guidelines over individual references. Although we reviewed articles and trials relevant to general critical illness, we preferred articles specific to ARDS. We added a small number of key references published after January 2024 that have implications for clinical practice.

Historical perspective and updated definition

ARDS was first described in a case series of 12 published in *The Lancet* by Ashbaugh and colleagues in 1967.[9] Defining characteristics of the syndrome as described in that series were the occurrence of tachypnea, hypoxemia, and reduced lung compliance after a predisposing insult. The authors also noted patchy bilateral infiltrates on chest radiography that closely resembled hydrostatic pulmonary edema. Autopsy samples among the seven deceased patients showed inflammation, alveolar edema and collapse, interstitial edema, and hyaline membranes in six of the seven patients.[9] In this series, despite the therapeutic

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benefit of positive pressure ventilation, the level of respiratory support needed was not considered a defining feature of the syndrome; in fact, two of the patients included in the series were on room air.[9]

The criteria for defining ARDS have changed, with varying degrees of importance placed on the role of positive pressure ventilation. In 1988 Murray and colleagues introduced the Lung Injury Score.[10] This score is calculated on the basis of a four point score of the severity of radiographic abnormality, hypoxemia, amount of positive end expiratory pressure (PEEP) in mechanically ventilated patients, and lung compliance when measured. Any combination of severe abnormalities resulting in a score >2.5 constitutes ARDS under this definition, even in the absence of positive pressure ventilation or a lung compliance measurement.[10] In 1994 the AECC further refined the definition of ARDS and introduced "acute lung injury" to describe patients with less severe hypoxemia. This definition specified that the parenchymal injury must be acute, that edema cannot be the result of elevated left atrial pressure, that severity should be stratified by the ratio of partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) (with the term "ARDS" reserved for only more severe hypoxemia with PaO_2/FiO_2 ≤200 mm Hg) regardless of the presence or absence of applied PEEP.[11] The 2012 Berlin definition introduced a conceptual model of ARDS, specified the timeline of "acute" parenchymal injury to be within seven days, eliminated acute lung injury in favor of mild, moderate, and severe ARDS, and required that ≥5 cm H_2O of PEEP be applied by invasive or non-invasive mechanical ventilation.[12]

A consensus conference in 2023 proposed an expanded global definition of ARDS (fig 1) that includes patients receiving high flow nasal oxygen (HFNO), allows for the diagnosis of ARDS using pulse oximetry without the requirement for an arterial blood gas, allows thoracic ultrasonography in the absence of availability of chest radiography, and formally incorporates the Kigali modification of the Berlin definition for resource limited areas.[8 13] The rationale for this expansion is delineated in detail by the authors and includes that the clinical use of HFNO has expanded such that it is the preferred mode of support for some patients with hypoxemia and bilateral opacities who would previously have been managed with an endotracheal tube and that the Berlin definition restricts the diagnosis of ARDS to settings in which advanced diagnostic and support modalities are available.[8 14-16] Limitations of the global definition include lack of validation in large cohorts of patients and ongoing uncertainty about what constitutes the "gold standard" for identifying ARDS.[17] However, most patients not receiving positive pressure ventilation continue to fulfill criteria for ARDS after initiation of ventilation.[18] In addition, expanding the definition of covid-19 related ARDS to include patients being treated with HFNO did not negatively affect the definition's predictive validity for mortality.[19]

Epidemiology

Population based studies since the publication of the AECC definition have varied widely in their estimates of the incidence of ARDS, ranging from 3.65 to 78.9 per 100 000 person years.[20] Hospital based studies similarly vary, with estimated incidence among admissions ranging from as low as 1.3% to as high as 19%.[20 21] The epidemiology of Berlin defined ARDS among patients in the intensive care unit (ICU) before the covid-19 pandemic was most extensively studied in the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG-SAFE),[2] which included almost 30 000 patients in 459 ICUs across 50 countries over a four week period in 2014. This study estimated that the incidence of Berlin defined ARDS was 10.4% among patients in ICU and 23.4% among mechanically ventilated patients, with mortality rates of 40% overall and 34.9%, 40.3%, and 46.1% for mild, moderate, and severe ARDS, respectively, although the attributable mortality from ARDS is lower.[2 22] Some studies have found that mortality related to non-covid ARDS has remained relatively static over time at about 30-35% for mild ARDS and 45-50% for severe ARDS,[2 20 21 23-28] despite changes in standard management. However, other studies have found an overall decrease in mortality rates for ARDS.[29-31] Adult patients with ARDS are more frequently male than female, with average ages falling in the sixth and seventh decades of life in most studies.[2 21 29 32-34] Studies that include race (US based) before covid-19 have generally found that about 70-75% of patients who develop ARDS are white.[33 35 36] A US study in 2009 reported a higher mortality among black and Hispanic patients with acute lung injury from the ARDS Network.[37] Data on race and ethnicity are often not reported in studies outside the US.

The covid-19 pandemic altered the epidemiology of ARDS, with one estimate indicating a 10-fold increase in the incidence of ARDS with covid-19 in the US from March 2020 through February 2022.[38] Another study found that deaths from ARDS in the US almost quintupled from 2019 to 2020 and that covid-19 was diagnosed in 81% of patients who died with ARDS in 2020.[4] The incidence of ARDS among patients with covid-19 in ICU was higher than that of the general ICU population, ranging from approximately 50% to 80%.[19 39 40] Estimates of mortality from covid-19 ARDS vary widely by region, but a global pooled estimate found that covid-19 ARDS has a mortality rate of 39%, similar to that of non-covid ARDS,[2 41] which is in keeping with estimates from several other studies.[19 39 40] Patients with covid-19 ARDS were predominantly male with a similar average age to those with non-covid ARDS.[19 39 42] In the US, a lower proportion of patients with covid-19 ARDS were white than in non-covid ARDS.[19 43] How the incidence and outcomes of non-covid ARDS changed during the covid-19 pandemic is not well understood.

The new global definition of ARDS will undoubtedly affect the epidemiology of ARDS.

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Conceptual model: ARDS is an acute diffuse, inflammatory lung injury precipitated by a predisposing risk factor such as pneumonia, non-pulmonary infection, trauma, transfusion, burn, aspiration, or shock. The resulting injury leads to increased pulmonary vascular and epithelial permeability, lung edema, and gravity dependent atelectasis, all of which contribute to loss of aerated lung tissue. The clinical hallmarks are arterial hypoxemia and diffuse radiographic opacities associated with increased shunting, increased alveolar dead space, and decreased lung compliance. The clinical presentation is influenced by medical management (position, sedation, paralysis, and fluid balance). Histological findings vary and may include intra-alveolar edema, inflammation, hyaline membrane formation, and alveolar hemorrhage.

Criteria that apply to all ARDS categories

Risk factors and origin of edema

Precipitated by an acute predisposing risk factor such as pneumonia, non-pulmonary infection, trauma, transfusion, aspiration, or shock. Pulmonary edema is not exclusively or primarily attributable to cardiogenic pulmonary edema/fluid overload, and hypoxemia/gas exchange abnormalities are not primarily attributable to atelectasis. However, ARDS can be diagnosed in the presence of these conditions if a predisposing risk factor for ARDS is also present.

Timing

Acute onset or worsening of hypoxemic respiratory failure within 1 week of the estimated onset of the predisposing risk factor or new or worsening respiratory symptoms.

Chest imaging

Bilateral opacities on chest radiograph, computed tomography, or ultrasonography* not fully explained by effusions, atelectasis, or nodules/masses.

Criteria that apply to specific ARDS categories

	Non-intubated ARDS	Intubated ARDS	Modified definition for resource variable settings¶
Oxygenation†‡	$PaO_2/FiO_2 \leq 300$ mm Hg or $SpO_2/FiO_2 \leq 315$ mm Hg (if $SpO_2 \leq 97\%$) on HFNO with a flow of ≥30 L/min or NIV/CPAP with ≥5 cm H_2O expiratory pressure	**Mild§:** $200 < PaO_2/FiO_2 \leq 300$ or $235 \leq SpO_2/FiO_2 \leq 315$ (if $SpO_2 \leq 97\%$) **Moderate:** $100 < PaO_2/FiO_2 \leq 200$ or $148 < SpO_2/FiO_2 \leq 235$ (if $SpO_2 \leq 97\%$) **Severe:** $PaO_2/FiO_2 \leq 100$ or $SpO_2/FiO_2 \leq 148$ (if $SpO_2 \leq 97\%$)	$SpO_2/FiO_2 \leq 315$ (if $SpO_2 \leq 97\%$).** End expiratory pressure or a minimum flow rate of oxygen is not required for diagnosis in resource variable settings

Differences from Berlin definition

- Conceptual model emphasizes the importance of management on the progression of ARDS and histological variability
- New category of "non-intubated ARDS" includes patients supported with HFNO
- SpO_2/FiO_2 may be used to classify hypoxemia severity when $SpO_2 \leq 97\%$
- Lung ultrasonography may be used to diagnose bilateral non-cardiogenic pulmonary edema
- A definition for resource variable settings that does not require a minimum level of respiratory support is formally adopted

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Fig 1 | Diagnostic criteria for global definition of acute respiratory distress syndrome (ARDS). CPAP=continuous positive airway pressure; FiO_2=fraction of inspired oxygen; HFNO=high flow nasal oxygen; NIV=non-invasive ventilation; PaO_2=partial pressure of oxygen; PEEP=positive end expiratory pressure; SpO_2=pulse oximetric oxygen saturation. *Ultrasonography operator should be well trained in use of ultrasonography for identifying pulmonary infiltrates. †Blood gas and oximetry measurements should be made when patient is comfortably at rest and ≥30 min after changes in position, FiO_2, or flow rate. For pulse oximetry, ensure adequate waveform and oximeter placement. SpO_2/FiO_2 is not valid above saturation values of 97%. Pulse oximetry is not recommended for diagnosis if hemoglobin abnormality is suspected (eg, methemoglobinemia or carboxyhemoglobinemia). ‡If altitude is >1000 m, apply correction factor = (PaO_2 or SpO_2)/FiO_2×(barometric pressure/760). §For all severity categories of intubated ARDS, a minimum PEEP of 5 cm H_2O is required. Patients may move from one category to another throughout their disease course. ¶Modified oxygenation criteria can be applied in settings where arterial blood gas or HFNO, NIV, and mechanical ventilation are not routinely available. **Estimated FiO_2=ambient FiO_2 (eg, 0.21)+0.03×O_2 flow rate (L/min). Adapted with permission from Matthay et al[8]

Because of the formal adoption of the Kigali modification,[13] diagnosing ARDS will be feasible in settings where diagnosis was previously not possible because of technological constraints.[8 15 44] For example, LUNG-SAFE did not include data from low income countries.[2] However, the ICU and hospital level variability in practice that has made standardizing estimates of ARDS challenging under the current definition may be exacerbated.[45] In the initial description of the Kigali modification, the incidence of ARDS in hospitals increased from 0% using the Berlin definition to 4% using the modified definition, with a mortality rate of 50%.[13] Secondly, the overall incidence of ARDS will likely increase with the inclusion of patients on HFNO. In the case of covid-19, one study found that expanding

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the criteria for ARDS to include patients on HFNO increased the incidence from 22% to 29%.[19] An updated understanding of the global epidemiology of ARDS, perhaps with the assistance of artificial intelligence based estimates, is an important priority for investigators.

Risk factors

Risk factors for the development of ARDS can be considered in two categories: proximal risk factors (that is, those that predispose to the development of ARDS within the traditional seven day window) and background risk factors including demographics, medical comorbidities, and environmental exposures.

Proximal risk factors

The most common proximal cause of ARDS is infection, either pulmonary or non-pulmonary, with aspiration, multiple transfusions, trauma, and pancreatitis as less common causes in most epidemiological studies.[2 25 29 34 46 47] Some studies have found that the overall incidence of ARDS associated with trauma has decreased,[48 49] although others have found no change.[50] The incidence of transfusion related acute lung injury (TRALI) has decreased in countries where the use of male predominant plasma has increased.[51] One study found that approximately 5-10% of cases of ARDS are associated with uncommon risk factors such as tumor, immune injury, and drug toxicity and that about 2.5% of cases are idiopathic.[46] Few studies have looked at the incidence of and risk factors for ARDS outside high income countries, but the limited existing data suggest that infection remains the most common predisposing risk factor in low and middle income countries[13 23 52]; however, pathogens such as plasmodium species, dengue virus, and leptospirosis are more common in these settings than in high income countries.[53-56] Trauma is also a more common risk factor in low and middle income countries than in high income countries,[13 57] and strategies to limit TRALI have not been implemented in much of the developing world.[51]

Background risk factors

Demographics

Patient specific and population specific factors also inform the risk of development of ARDS. Before the covid-19 pandemic, data about the role of older age, race and ethnicity, and sex in both the development of and outcomes from ARDS among people at risk were conflicting.[32 33 58-67] In covid-19, older age and male sex were clear risk factors for the development of severe disease, including ARDS.[43 68-72] The influence of race and ethnicity on the development of ARDS related to covid-19 is less clear after adjustment for other factors,[43 68 73 74] perhaps because the effect of race depends in turn on other factors such as regional differences in access to healthcare and risk of exposure.[75] Beyond traditional demographic considerations, evidence also suggests that genetic factors contribute to the risk of developing ARDS and its outcomes.[76]

Comorbidities

Several medical comorbidities are more common among patients with ARDS than in the general population. For example, 21% of patients in LUNG-SAFE had diabetes compared with an age standardized global prevalence of <10%.[2 77] The prevalences of chronic obstructive pulmonary disease and chronic heart failure among patients in LUNG-SAFE were similarly approximately twice the global prevalence.[2 78 79] Chronic medical comorbidities, especially malignancy and immunosuppression, are known risk factors for adverse outcomes from critical illness.[80-84] Diabetes and obesity merit particular consideration for non-covid related versus covid related ARDS because of their seemingly divergent effects on outcomes by cause. Diabetes is not consistently associated with mortality from non-covid ARDS, although data are conflicting.[80 85-90] Overweight and obesity have been observed to be associated with an increased risk of incident ARDS,[91] but they are associated with lower mortality in many studies of non-covid ARDS with the exception of that caused by trauma.[92-97] This association with lower mortality is not observed in covid-19 ARDS,[98] with some studies showing that diabetes and obesity are associated with an increased risk of severe covid-19 and death,[39 99-104] although this effect may differ by age.[105] Patients with obesity are more likely to be subject to inappropriately high tidal volumes.

Environmental exposures

Certain exposures, such as to air pollution, alcohol, and cigarette smoke, also contribute to the risk of ARDS.[106] An emerging connection has been identified between risk and outcomes of ARDS and ambient particulate matter and gaseous pollutants,[107-110] including adverse outcomes from covid-19.[111-114] Chronic alcohol use also predisposes to both non-covid ARDS and covid-19 ARDS.[115-118] Cigarette smokers are at risk for adverse outcomes of ARDS at comparably lower severity levels than are non-cigarette smokers.[106 119 120] Emerging evidence on the role of tobacco smoking in covid-19 suggests that cigarette smoking increases the risk of severe covid-19 and death, although the incidence of initial SARS-CoV-2 infection among smokers may be lower.[121-123] Overall, the predisposition to developing ARDS and related adverse outcomes is complex and depends on the interplay among personal susceptibility, individual exposures, population level risk factors, and the environment.

Pathophysiology

The pathophysiology of ARDS involves disruption of the alveolar capillary-epithelial barrier, impaired alveolar fluid clearance, dysregulation of the host immune response, and oxidative and mechanical stress (fig 2).[1] Either lung epithelial injury in the setting of a direct pulmonary insult (for example,

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pneumonia or aspiration pneumonitis) or lung endothelial injury in the setting of systemic illness (for example, non-pulmonary sepsis or TRALI) may be the inciting event for ARDS and contribute to its severity.[124 125] Epithelial injury propagates the pro-inflammatory and pro-coagulant cascade of pulmonary injury.[126] It also depletes surfactant producing type II cells and contributes to surfactant dysfunction, promoting worsening atelectasis and susceptibility to superinfection.[127 128] The pulmonary epithelium is also crucial to the resolution of pulmonary edema[129]; impairment of clearance of alveolar fluid is correlated with the severity of shock and clinical outcomes in ARDS.[130 131] How the alveolar epithelium responds to injury and is able to re-establish an effective barrier is an area of active study. Injury to and activation of the pulmonary vascular endothelium through cell death, disruption of intercellular junctions, and alteration in cell signaling pathways facilitates the exudation of protein-rich edema fluid.[1 132] Endothelial injury also promotes adhesion and activation of neutrophils and platelets as well as the formation of pulmonary microthrombi that increase dead space ventilation.[133-136]

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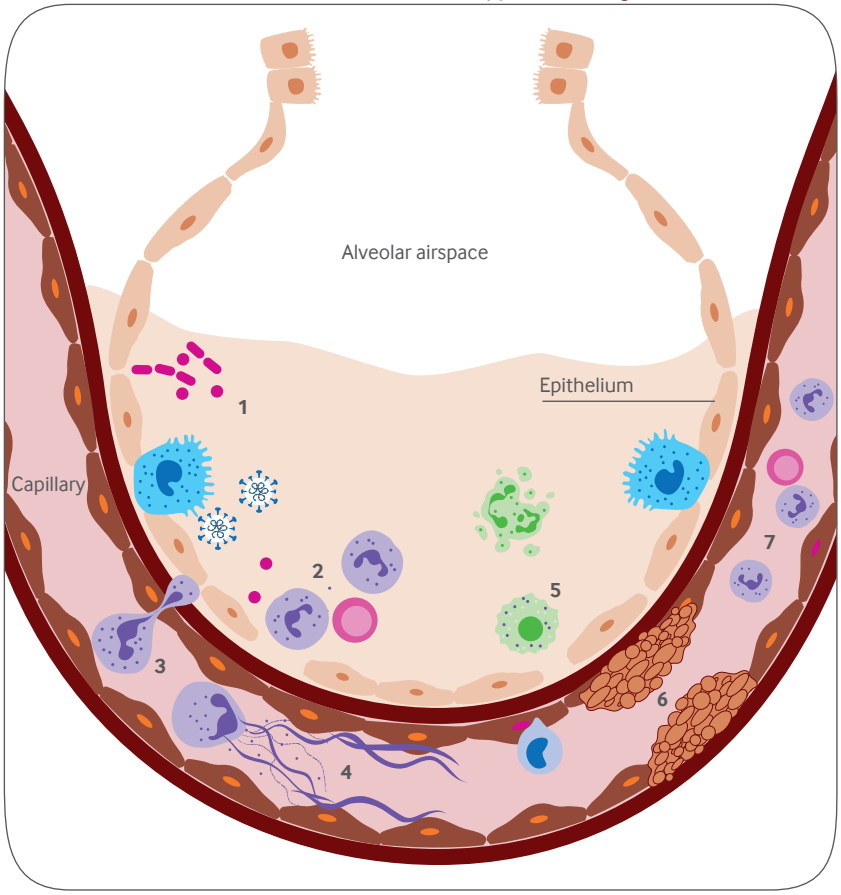

Fig 2 | Model of pathogenesis of acute respiratory distress syndrome with a focus on pneumonia. 1) Early bacterial or viral injury to the alveolar epithelium facilitates formation of protein-rich pulmonary edema, impairs surfactant production and alveolar fluid clearance, and initiates an inflammatory cascade. 2) Recruited immune cells are often functionally impaired and pathogen clearance is reduced. 3) Epithelial injury potentiates endothelial injury. Neutrophils migrate to sites of tissue damage and recruit macrophages. 4) Neutrophil extracellular traps promote platelet aggregation. 5) M1 macrophages promote ongoing inflammation. Phagocytosis of apoptotic neutrophils may be impaired. 6) Thrombi form in the pulmonary microvasculature. 7) Systemic inflammation is characterized by peripheral neutrophilia and lymphopenia, especially in viral infections such as covid-19

As in other critical illness syndromes such as sepsis,[137] the normally protective host response can become dysregulated in ARDS contributing to further organ injury. Neutrophil recruitment to the lung is an important event in the development of many cases of ARDS, although the syndrome can occur in the absence of neutrophilic infiltration in profoundly neutropenic patients.[138-140] Neutrophils aggregate with platelets to promote lung injury, elaborate potentially harmful neutrophil extracellular traps, and are a source of reactive oxygen species and proteinases that contribute to tissue damage.[138 141-145] The inflammatory process driving organ injury in ARDS is complex and also involves adaptive immunity, including the balance between pro-inflammatory and pro-resolving T cell phenotypes.[146] Circulating non-immune cells also contribute to the pathogenesis of inflammation in ARDS. An emerging area of interest in ARDS is the role of the red blood cell and cell-free hemoglobin in promoting oxidative stress, vascular permeability, and immune cell recruitment.[147] Higher plasma concentrations of cell-free hemoglobin in patients with ARDS have been associated with death, and oxidative stress in this setting may be attenuated by paracetamol (acetaminophen) treatment.[148-150]

Early in the covid-19 pandemic, some experts posited that covid-19 ARDS represented a distinct pathophysiological and clinical entity with unique sub-phenotypes,[151] in some cases warranting a fundamentally different management approach from "traditional" ARDS.[152] Clinical and pathophysiological heterogeneity is not unique to covid-19 ARDS,[153] and further investigation has shown that the respiratory physiology of covid-19 ARDS is likely similar to that of other causes of ARDS.[154-156] However, some pathophysiological features are more pronounced in severe covid-19 than in other causes of ARDS, including other viral infections.[3] In particular, patients with severe covid-19 have marked endothelial dysfunction and coagulation abnormalities, as well as an immune response characterized by myeloid inflammation, neutrophilia, lymphopenia, and functional dysregulation of adaptive immunity.[157-161] Plasma biomarker analyses suggest that lung epithelial injury early in the course of covid-19 precedes this endothelial dysfunction and inflammation.[162-164] As with other causes of ARDS, however, the organ injury signature in peripheral blood likely differs from that in the distal airspaces.[165-167] Although some authors have characterized the peripheral inflammatory signature of covid-19 as a "cytokine storm,"[168] circulating inflammatory signatures as measured by circulating protein biomarkers or gene expression

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analysis in patients with covid-19 are lower than those in patients with "classical" ARDS.[169]

Such differences underscore the importance of understanding critical illness syndromes such as ARDS by studying both their biology and their clinical presentation. For example, two biological phenotypes of ARDS, "hyper-inflammatory" and "hypo-inflammatory," have been consistently identified in both clinical trials and observational cohorts.[170-176] The hyper-inflammatory phenotype is characterized by a distinct gene expression signature,[177] higher concentrations of circulating pro-inflammatory cytokines such as interleukin 6, interleukin 8, and soluble tumor necrosis factor receptor-1 and has higher mortality rates than the hypo-inflammatory phenotype.[178] These phenotypes are associated with differential responses to fluid management, PEEP, simvastatin therapy, and corticosteroid treatment in secondary analyses and might provide a basis for future clinical trial enrichment,[170 171 177 179] but they require prospective validation.

Pathology

The pathology of ARDS is classically described as a diffuse alveolar damage (DAD) pattern characterized by protein-rich intra-alveolar edema, hyaline membrane formation, neutrophil infiltration, and alveolar hemorrhage.[12] Animal models of ARDS often seek to replicate this pattern.[180] DAD is not universal among patients with clinical ARDS, however,[181] as acknowledged in the recently proposed global definition of ARDS.[8] One challenge for better understanding the spectrum of histological manifestations of ARDS is that few patients undergo tissue sampling,[182] and lung biopsy is often restricted to those with unresolving ARDS or ARDS of unknown cause.[183] Other studies of the pathology of ARDS rely on autopsy series, which may not reflect the histological changes in non-fatal cases.[181 184] DAD is more common among patients with severe ARDS and is associated with worse respiratory system compliance, oxygenation, and overall illness severity, including higher mortality.[185] Clinical characteristics do not consistently predict the presence of DAD,[185 186] however, and DAD is present in only approximately half of cases of severe ARDS.[181 183 185] As histological changes in ARDS are not necessarily uniform, lung biopsy might not capture DAD in every case in which it is present, making consistent clinical correlations even more difficult. One study showed that high resolution computed tomography findings of a "geographic" pattern of lung injury in combination with elevated concentrations of circulating Krebs von den Lungen-6, a marker of type II alveolar epithelial cell injury, was highly specific for DAD.[187] Better methods for identifying clinical correlates of histological ARDS findings could be useful in identifying effective therapies and require further study.[188]

Management

Critical care interventions

The cornerstone of ARDS management is effective comprehensive critical care interventions (table 1), many of which, in contrast to pharmacologic interventions, have consistently been associated with reduced mortality and duration of mechanical ventilation (fig 3). Thus, clinicians need to recognize ARDS early and appropriately implement mortality reducing interventions such as lung protective

Table 1 | Landmark trials informing critical care management of patients with acute respiratory distress syndrome (ARDS)

Trial	Publication year	Intervention	Principal findings	Implications for management
Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome (ARMA)[6]	2000	Tidal volume of 12 mL/kg PBW and plateau pressure of ≤50 cm H_2O *v* 6 mL/kg PBW and plateau pressure of ≤30 cm H_2O	8.8% lower mortality before discharge in lower tidal volume group than in higher tidal volume group	LTV ventilation should be applied for all patients with ARDS
Higher versus Lower Positive End-Expiratory Pressures in Patients with the Acute Respiratory Distress Syndrome (ALVEOLI)[189]	2004	Higher PEEP *v* lower PEEP titrated on basis of Fi_02	No difference in primary outcome of proportion discharged alive and breathing without assistance or any secondary outcome	Patients can be managed with use of higher or lower PEEP strategy
Comparison of Two Fluid Management Strategies in Acute Lung Injury (FACTT)[190]	2006	Factorial assignment to central venous or pulmonary artery catheter and conservative or liberal fluid strategy	No difference in primary outcome of 60 day mortality, but more ventilator-free days and ICU-free days to day 28	Patients likely benefit from even-to-negative fluid balance after initial resuscitation
Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome (ACURASYS)[191]	2010	Cisatracurium besylate *v* placebo within 48 h of onset of severe (PaO_2/FiO_2 <150 mm Hg) ARDS	Higher adjusted 90 day survival (HR 0.68, 95% CI 0.48 to 0.98) in intervention arm	Neuromuscular blockade was recommended before publication of ROSE trial (below)
Prone Positioning in Severe Acute Respiratory Distress Syndrome (PROSEVA)[192]	2013	Prone positioning for ≥16 h/day in moderate to severe (PaO_2/FiO_2 <150 mm Hg) ARDS until improvement in oxygenation *v* remaining supine	16.8% lower 28 day mortality (primary outcome) and 17.4% lower 90 day mortality (secondary outcome) in intervention arm	Prone positioning is recommended for ARDS with PaO_2/FiO_2 <150
High-Flow Nasal Oxygen through Nasal Cannula in Acute Hypoxemic Respiratory Failure (FLORALI)[193]	2015	HFNO *v* standard oxygen therapy *v* NIPPV for non-hypercapnic patients with PaO_2/FiO_2 ≤300 mm Hg; 79% had bilateral infiltrates	Lower mortality at 90 days in HFNO group compared with both NIPPV and standard oxygen. Lower rate of intubation in HFNO group compared with either NIPPV or standard oxygen when PaO_2/FiO_2 ≤200 mm Hg	HFNO is a safe way to manage patients with hypoxemic respiratory failure/non-intubated ARDS

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Table 1 | (Continued)

Trial	Publication year	Intervention	Principal findings	Implications for management
Effect of Noninvasive Ventilation versus Oxygen Therapy on Mortality Among Immunocompromised Patients With Acute Respiratory Failure (IVNICTUS)[194]	2015	NIPPV *v* standard oxygen therapy for non-hypercapnic, immunocompromised patients with respiratory failure (PaO_2 <60 mm Hg on room air, or tachypnea >30/min, or labored breathing or respiratory distress or dyspnea at rest)	No statistical difference in primary endpoint of 28 day mortality or secondary outcomes, including intubation rate	NIV is not different from standard oxygen therapy for immunocompromised patients with hypoxemic respiratory failure with respect to clinical outcomes
Effect of High-Flow Nasal Oxygen versus Standard Oxygen on 28-Day Mortality in Immunocompromised Patients With Acute Respiratory Failure (HIGH)[195]	2018	HFNO *v* standard oxygen therapy for non-hypercapnic, immunocompromised patients with respiratory failure (PaO_2 <60 mm Hg or SpO_2 <90% on room air, or tachypnea >30/min or labored breathing or respiratory distress, and need for oxygen ≥6 L/min)	No statistical difference in primary endpoint of 28 day mortality or any secondary outcomes	HFNO is not different from standard oxygen therapy for immunocompromised patients with hypoxemic respiratory failure with respect to clinical outcomes
Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA)[196]	2018	ECMO *v* conventional treatment for very severe ARDS (PaO_2/FiO_2 <60 mm Hg for 3 h or <80 mm Hg for 6 h or arterial blood pH <7.25 with $PaCO_2$ ≥60 for 6 h). Crossover permitted for rescue therapy	No statistical difference in primary endpoint of 60 day mortality (35% in ECMO group *v* 46% in control group; P=0.09). High rate of crossover (28%) in conventional therapy group	ECMO remains an important option for rescue therapy in refractory cases of ARDS
Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome (ROSE)[190]	2019	Cisatracurium infusion with deep sedation for 48 h *v* usual care with light sedation targets. High PEEP strategy used for all patients	No between group differences for primary endpoint of 90 day hospital mortality or any secondary outcome. 17% crossover rate and low use of prone positioning (15.8%). Higher rate of serious cardiovascular events in NMB group	NMB recommendations differ, but certainty of evidence is low. Other routine supportive measures, including prone positioning, should be prioritized. NMB might provide benefit in early severe ARDS
Liberal or Conservative Oxygen Therapy for Acute Respiratory Distress Syndrome ($LOCO_2$)[197]	2020	PaO_2 target of 90-100 mm Hg *v* 55-70 mm Hg	Trial stopped early by DSMB because of possibility of harm in conservative oxygen group. No difference in primary outcome of 28 day mortality but significantly higher 90 day mortality in conservative group (44.4% *v* 30.4%) and higher rate of mesenteric ischemia in conservative group (5 *v* 0 events)	A conservative arterial PaO_2 target of 55-70 mm Hg is not beneficial and may be harmful in ARDS
Effect of Lower Tidal Volume Ventilation Facilitated by Extracorporeal Carbon Dioxide Removal versus Standard Care Ventilation on 90-day Mortality in Patients with Acute Hypoxemic Respiratory Failure (REST)[198]	2021	Target tidal volume of 3 ml/kg PBW facilitated by $ECCO_2R$ *v* standard LTV ventilation in patients with PaO_2/FiO_2 ≤150 mm Hg not caused by cardiogenic pulmonary edema. Approximately 60% had ARDS at enrollment	Trial stopped early by DSMB for futility and lack of feasibility to continue trial. Increased rate of severe adverse events including intracranial hemorrhage in intervention group, though this was not cited as reason for stopping trial. Results similar in ARDS subgroup	There is no benefit to and possible harm from extra-LTV ventilation facilitated by $ECCO_2R$ compared with standard LTV ventilation
Lower or Higher Oxygenation Targets for Acute Hypoxemic Respiratory Failure (HOT-ICU)[199]	2021	Target PaO_2 of 60 mm Hg *v* 90 mm Hg among hypoxemic patients receiving ≥10 L/min oxygen in open system or FiO_2 of 0.50 in closed system	No difference in primary outcome of 90 day mortality or in secondary outcomes. No difference in adverse events including mesenteric ischemia. Median achieved arterial oxygenation in lower target group was 70 mm Hg *v* 93.3 mm Hg in higher target group	A second trial confirming no benefit of a lower oxygen target compared with higher
High-flow nasal oxygen alone or alternating with non-invasive ventilation in critically ill immunocompromised patients with acute respiratory failure (FLORALI-IM)[200]	2022	HFNO alone *v* HFNO alternating with NIV for non-hypercapnic, immunocompromised patients with respiratory failure (respiratory rate of ≥25 breaths/min and PaO_2/FiO_2 ≤300 mm Hg)	No difference in primary outcome of 28 day mortality or any secondary outcomes except for comfort (less discomfort in HFNO group)	HFNO among immunocompromised patients with hypoxemic respiratory failure does not differ from alternating HFNO and NIV in terms of clinical outcomes and can be favored for patient comfort

CI=confidence interval; DSMB=data and safety monitoring board; $ECCO_2R$=extracorporeal carbon dioxide removal; ECMO=extracorporeal membrane oxygenation; FiO_2=fraction of inspired oxygen; HFNO=high flow nasal oxygen; HR=hazard ratio; ICU=intensive care unit; LTV=low tidal volume; NIPPV=non-invasive positive pressure ventilation; NIV=non-invasive ventilation; NMB=neuromuscular blockade; $PaCo_2$=partial pressure of carbon dioxide; PaO_2=partial pressure of oxygen; PBW=predicted body weight; PEEP=positive end expiratory pressure; SpO_2=oxygen saturation.

ventilation and prone positioning.[201 202] Lung protective ventilation with low tidal volume (6 mL/kg predicted body weight) and a plateau airway pressure below 30 cm H_2O reduces mortality from ARDS and should be universally applied in patients with known or suspected ARDS.[203] Inconsistent application of low tidal volume ventilation results in meaningful differences in adverse outcomes such as prolonged intubation and mortality.[187] Although this would seem to be a pulmonary specific intervention, the application of lower tidal volumes also attenuates the systemic inflammatory response.[204 205] Ventilator management of tidal volumes should not meaningfully differ in patients with covid-19 ARDS.[206]

Low tidal volume ventilation does not entirely mitigate the risk of ventilator induced lung injury. A trial of ultra-low tidal volume ventilation facilitated by extracorporeal removal of carbon dioxide found no mortality benefit.[198] This trial did not meet its target enrollment and had several limitations including low use of prone positioning, a low rate of

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enrollment versus patients screened, and a large non-ARDS population. In addition, several parameters in the intervention group suggested inefficient CO_2 removal.[207] A more targeted trial using a more efficient device for CO_2 removal is needed. Other strategies for improved ventilator management, such as limiting driving pressure, varying tidal volumes to avoid possibly injurious effects of consistent tidal volume ventilation,[208] and personalizing PEEP to surrogate measurements of pleural pressure or radiographic features, have also not improved mortality in clinical trials.[189] Aggressive recruitment maneuvers using sustained delivery of very high PEEP are injurious and should be avoided.[209-211]

ARDS can sometimes be managed with non-invasive respiratory support. HFNO in patients with acute hypoxemic respiratory failure (AHRF), some of whom met clinical criteria for ARDS,[8] reduced mortality in a large clinical trial compared with non-invasive ventilation (NIV) via facemask or conventional oxygen therapy (COT).[193] A post hoc analysis of this trial found possible evidence of harm from NIV, but current evidence does not support extrapolation of these results to immunocompromised patients.[194 195 200 212] Before the covid-19 pandemic, a systematic review and meta-analysis including 3804 participants with AHRF found that helmet and facemask NIV were associated with a lower risk of mortality compared with COT, whereas HFNO was not.[213] This meta-analysis included participants with exacerbations of chronic obstructive pulmonary disease or heart failure as their cause of respiratory failure, although trials primarily focused on these causes were excluded. A more recent systematic review and meta-analysis of non-invasive oxygen in AHRF, including studies of participants with covid-19 respiratory failure and excluding studies focused on participants enrolled in the emergency department and postoperatively, identified a probable mortality benefit of helmet continuous positive airway pressure (CPAP) and possible benefit of HFNO and both face mask and helmet NIV compared with COT.[214] Dedicated trials of non-invasive oxygen delivery in covid-19 have identified a likely benefit of early CPAP therapy but not helmet NIV compared with COT.[215 216]

In the most severe cases of ARDS, veno-venous extracorporeal membrane oxygenation (ECMO) can be used as rescue therapy. An international RCT (EOLIA) of veno-venous ECMO for severe ARDS (PaO_2 ≤50 mm Hg for three hours, ≤80 mm Hg for six hours, or hypercarbia with acidemia) compared with usual

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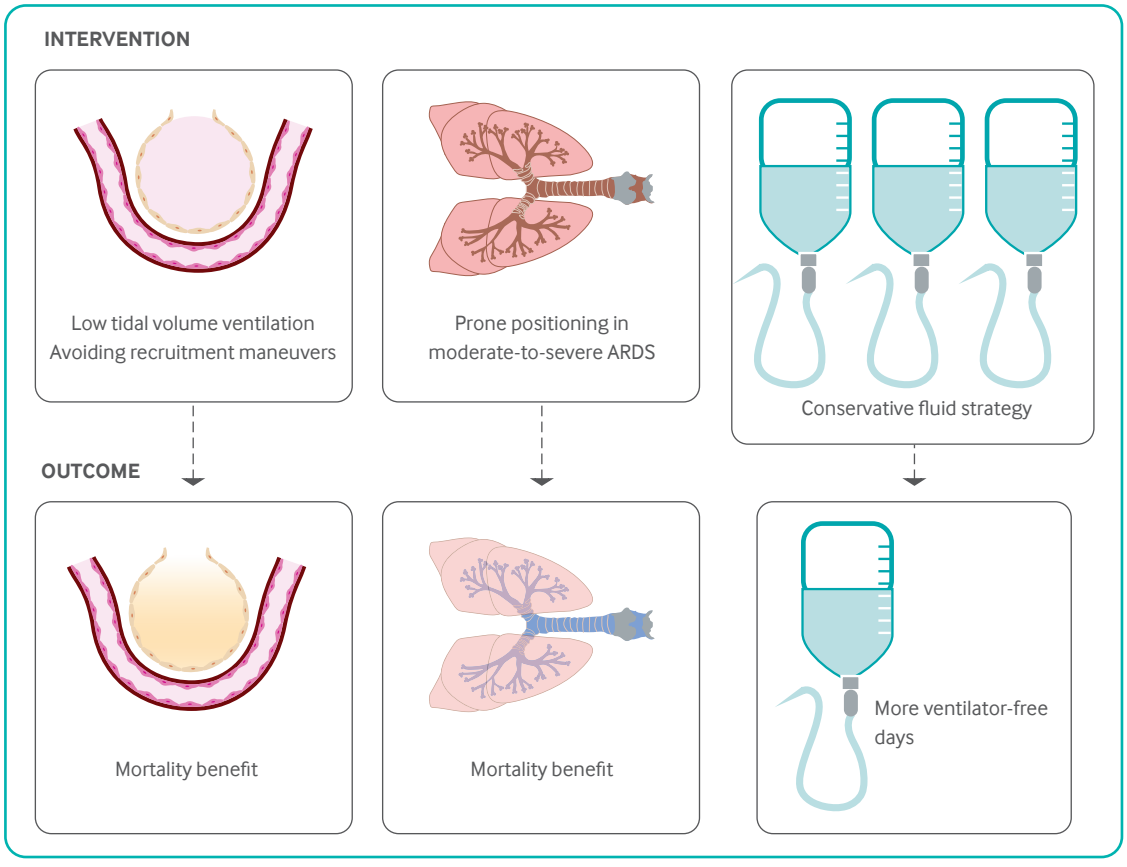

Fig 3 | Interventions to improve outcomes in acute respiratory distress syndrome (ARDS). Interventions that have been shown to improve clinical outcomes in ARDS include lung protective low tidal volume plateau pressure limited ventilation, prone positioning for moderate to severe hypoxemia, and fluid conservative therapy once shock is resolved

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care found no statistical mortality benefit but was stopped early. The point estimate favored ECMO therapy for the primary trial outcome of 60 day mortality with an upper 95% confidence bound of 1.04.[196] A subsequent systematic review and meta-analysis concluded that ECMO reduces 30 day and 60 day mortality, although the analysis is limited by the inclusion of only two RCTs.[217] Interpreting the utility of ECMO in covid-19 is difficult given the variability in practice for treating covid-19 ARDS early in the pandemic, whether because of strain on resources or because of the belief that covid-19 represented a novel ARDS phenotype. The evidence supporting the use of ECMO in covid-19 ARDS derives from observational studies and emulation trials, but as with ventilator management, the same principles guiding management of non-covid ARDS with ECMO should probably be applied to covid-19 ARDS.[218-220]

Excessive oxygen delivery is injurious to the lung in experimental models and might potentiate ventilator induced lung injury.[221 222] Clinical data on oxygen targets for patients in ICU with hypoxemic respiratory failure do not show a consistent benefit of conservative versus liberal oxygen therapy,[199 223-225] although frank hyperoxia seems to be harmful.[226] A secondary analysis of ARDSNet trials showed an association between above-protocol oxygen exposure (PaO_2 >88 mm Hg and FiO_2 >0.5) and adverse clinical outcomes[227]; however, a dedicated RCT of liberal versus conservative oxygen therapy in patients with ARDS was terminated early because conservative oxygen therapy compared with liberal oxygen therapy (target PaO_2 55-70 mm Hg or SpO_2 88-92% versus PaO_2 90-105 mm Hg or SpO_2 ≥96%) was associated with a signal for higher mortality and resulted in several mesenteric ischemic events.[197] A large observational study found that both hyperoxemia and hypoxemia were associated with adverse outcomes in ARDS, and that a target PaO_2 of approximately 100 mm Hg may be most favorable.[228]

Effective ventilator management can be supported by several strategies that have shown benefit in patients with ARDS. Prone positioning for at least 16 hours a day in patients with a PaO_2/FiO_2 <150 mm Hg reduces mortality by 17.4% compared with supine positioning and lung protective ventilation alone.[192] Prone positioning likely has a benefit even in non-intubated patients with covid-19 for avoiding endotracheal intubation.[229] A 2010 randomized trial of neuromuscular blockade for moderate-to-severe ARDS (ACURASYS) found an approximately 9% mortality benefit compared with no neuromuscular blockade[230]; however, a subsequent trial of neuromuscular blockade with deep sedation versus usual care using a high PEEP strategy and light sedation targets (ROSE) found no mortality benefit.[191] One limitation of the ROSE trial was the relatively low use of routine prone positioning, making a direct comparison with the ACURASYS trial challenging.[191] Therefore, the management guidelines on the use of neuromuscular blockade are not definitive. The most recent ARDS guidelines from the European Society of Intensive Care Medicine (ESICM) recommend against its routine use, whereas the American Thoracic Society (ATS) makes a conditional recommendation for neuromuscular blockade in early severe ARDS.[209 210] A restrictive fluid strategy with a goal of net even to negative fluid balance after initial resuscitation targets are met reduces the duration of mechanical ventilation and ICU stay in patients with non-covid ARDS,[190 191] and it is also beneficial in covid-19 ARDS.[231] Aside from "hard outcomes" such as mortality, comprehensive critical care should also prioritize the patient's experience by minimizing commonly reported distressing symptoms such as thirst, pain, and anxiety.[232]

Several areas of ARDS management warrant further study. These include the ideal timing, duration, and mode (for example, volume versus pressure controlled ventilation, or alternative ventilator modes such as airway pressure release ventilation) of both non-invasive respiratory support and invasive mechanical ventilation, especially as patients with severe hypoxemia are increasingly managed with non-invasive support modalities.

Pharmacologic management

No drug therapies have consistently shown benefit in all cases of ARDS. Reversible contributors should first be identified and treated. This is especially relevant for infectious causes for which antimicrobial or other therapy can be tailored to the offending pathogen or for which therapy differs from that for other causes of ARDS.[233] An emerging area of promising clinical research is the rapidly growing ability to identify the pathogen(s) responsible for ARDS—for example, by using real time rapid metagenomics in the ICU.[233 234] The list of agents that have been tested in ARDS is extensive, and this review will focus on a few select therapies of interest (table 2).

Statins

The 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) are an appealing candidate for ARDS therapy because they are inexpensive, are widely available, and act on many of the pathways that are implicated in the pathogenesis of ARDS.[241 242] Two large randomized controlled trials, one testing rosuvastatin (SAILS) and the other testing simvastatin (HARP-2), found no benefit of statin therapy on clinical outcomes in ARDS.[235 243] Simvastatin has also been tested in critically ill patients with covid-19 (not restricted to patients with ARDS, although almost all patients were receiving HFNO, NIV, or mechanical ventilation). The trial was terminated early because of low enrollment, but the results showed a high posterior probability of benefit.[236] Secondary analyses of the HARP-2 trial by severity of illness, ARDS phenotypes, and plasma interleukin 18 concentration suggest differential treatment effects that could inform future trial design.[170 175 244 245] No evidence was seen of a differential effect by ARDS phenotype in a secondary analysis of SAILS.[170 176] Other widely available

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Table 2 | Select trials of pharmacologic interventions for acute respiratory distress syndrome (ARDS) and severe pneumonia

Trial	Publication year	Intervention	Principal findings	Implications for management and further research
Rosuvastatin for Sepsis-Associated Acute Respiratory Distress Syndrome (SAILS)[235]	2014	40 mg loading dose followed by 20 mg daily rosuvastatin for up to 28 days *v* placebo in patients with Berlin defined ARDS	No difference in primary outcome of 60 day mortality. Fewer hepatic/renal failure-free days in rosuvastatin group	Rosuvastatin does not provide benefit in sepsis associated ARDS and might contribute to liver and kidney injury
Simvastatin in the Acute Respiratory Distress Syndrome (HARP-2)[236]	2014	80 mg simvastatin or placebo for up to 28 days in patients with Berlin defined ARDS	No difference in primary outcome of ventilator-free days. More treatment related adverse events in simvastatin group but similar number of serious adverse events	Simvastatin does not provide benefit in all cause ARDS
Randomized Clinical Trial of a Combination of an Inhaled Corticosteroid and Beta Agonist in Patients at Risk of Developing the Acute Respiratory Distress Syndrome (LIPS-B)[237]	2015	Nebulized budesonide/formoterol *v* placebo among hypoxemic patients in the emergency department with at least one risk factor for ARDS	Greater improvement in SaO_2/FiO_2 in intervention arm. No progression to ARDS in intervention group	Inhaled ICS/LABA warrants further investigation for prevention of ARDS
Dexamethasone Treatment for the Acute Respiratory Distress Syndrome (DEXA-ARDS)[238]	2020	20 mg dexamethasone daily on days 1-5 followed by 10 mg dexamethasone daily on days 6-10 in patients with established (after 24 h) moderate-to-severe ARDS compared with standard care	4.8 (95% CI 2.57 to 7.03) more ventilator-free days (primary outcome) in intervention group. Lower 60 day mortality in intervention group and no difference in adverse events	Early treatment with dexamethasone might benefit patients with established moderate-to-severe ARDS
Dexamethasone in Hospitalized Patients with COVID-19 (RECOVERY Dexamethasone)[239]	2021	6 mg dexamethasone daily for up to 10 days *v* usual care alone in patients admitted to hospital with covid-19	Lower 28 day mortality (primary outcome) in patients with any oxygen requirement, including mechanical ventilation (RR 0.64, 95% CI 0.51 to 0.81). No benefit in patients not requiring oxygen	Dexamethasone is beneficial and should be administered to patients with covid-19 ARDS
Hydrocortisone in Severe Community Acquired Pneumonia (CAPECOD)[240]	2023	Continuous infusion of 200 mg hydrocortisone/day for 4 days for followed by taper for total course of 8-14 days *v* placebo in patients with severe CAP. Patients with septic shock were excluded	Terminated early because of feasibility during covid-19 pandemic and evidence of benefit after second interim analysis. 5.4% lower 90 day mortality (primary outcome) and lower rates of endotracheal intubation and vasopressor initiation in hydrocortisone group	Although not specific to ARDS, some of the patients in CAPECOD met criteria for ARDS. Consider steroids in patients with non-covid ARDS due to severe CAP
Acetaminophen and Ascorbate in Sepsis: Targeted Therapy to Enhance Recovery (ASTER)[150]	2024	After closure of vitamin C arm, 1:1 randomization of patients with sepsis and hypotension or respiratory failure to 1 g paracetamol or placebo every 6 h for up to 5 days	Lower rate of ARDS development in paracetamol arm. Ascorbate arm closed because of evidence of harm in another large RCT of vitamin C in sepsis	Paracetamol may prevent development of ARDS in critically ill patients with sepsis. A larger trial is needed
Arrest Respiratory Failure from Pneumonia (ARREST PNEUMONIA)	Recruiting	Inhaled budesonide and formoterol *v* placebo every 12 h for 10 doses	Study recruiting	Study recruiting

CAP=community acquired pneumonia; FiO_2=fraction of inspired oxygen; ICS=inhaled corticosteroid; LABA=long acting β agonist; RCT=randomized controlled trial; RR=rate ratio; SaO_2=oxygen saturation.

drugs such as paracetamol, recently studied in the Acetaminophen for the Prevention and Treatment of Organ Dysfunction in Critically Ill Patients with Sepsis (ASTER) trial,[150] and inhaled corticosteroids/β agonists (NCT04193878) with indications outside of ARDS have been tested in ARDS and remain of interest not only for treatment but also for prevention.[246] In the ASTER trial, participants in the paracetamol arm developed ARDS at a significantly lower rate than did those in the placebo arm. This promising secondary outcome requires further validation.[150]

Corticosteroids

A major area of ongoing investigation is the use of systemic corticosteroids in ARDS. The benefit of corticosteroids in unselected patients with ARDS has been extensively studied with mixed results. A 2020 RCT of dexamethasone among patients with moderate-to-severe ARDS persisting for 24 hours or longer found a benefit in ventilator-free days and mortality, although the study did not meet its pre-specified enrollment.[237] Two larger trials, one in the UK (ISRCTN15076735) and one in the US (NCT05440851), will test dexamethasone in a larger group of participants with AHRF and/or ARDS. Heterogeneity in corticosteroid dosing, ARDS risk factors, and timing of administration make definitive conclusions about the use of steroids in all-comers with ARDS challenging, but the weight of the evidence suggests that they are likely beneficial in early ARDS.[238 247] The most recent ATS management guidelines for ARDS and the Society for Critical Care Medicine (SCCM) guidelines on the use of corticosteroids for sepsis, ARDS, and community acquired pneumonia (CAP) conditionally recommend the use of systemic corticosteroids in all patients with ARDS.[209] Corticosteroids are recommended in severe covid-19.[248] Suggested dosing regimens are available in the SCCM guidelines.[239]

Recently, two RCTs of corticosteroids in severe pneumonia, including patients with ARDS, came to differing conclusions about their benefit that are likely explained at least in part by differences in the study population and timing of steroid administration.[249 250] A trial of methylprednisolone in critically ill patients with CAP or hospital acquired

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pneumonia was terminated early for futility and found no benefit of methylprednisolone therapy on the primary outcome of 60 day mortality or any secondary outcomes.[249] This study allowed for steroid administration up to 96 hours after admission to hospital and included participants with septic shock, and almost all participants (96%) were male.[249] By contrast, a trial of early (within 24 hours of ICU presentation) hydrocortisone in severe CAP (70% male) that excluded patients with septic shock found a reduction in the primary study endpoint of 28 day mortality as well as in the rate of endotracheal intubation among patients who were not intubated at baseline.[250] A recent meta-analysis of the use of corticosteroids in CAP also found benefit in preventing progression to mechanical ventilation.[240] Recent animal data support these results.[251] Together, these studies suggest that in select patients with severe CAP, some of whom meet criteria for ARDS, corticosteroids are likely to provide benefit for preventing progression to mechanical ventilation and possibly for preventing death.

Prognosis and complications

Pulmonary dysfunction in ARDS is intimately connected with extrapulmonary organ dysfunction, especially of the brain, kidney, and heart. Extrapulmonary organ dysfunction is common in ARDS, with increasing prevalence as the severity of ARDS increases.[252] Patients with ARDS are at risk for delirium and long term cognitive impairment as a result of both ICU interventions and biological mechanisms.[253-256] Tackling delirium among patients with ARDS is an important priority, as its development is associated with long term cognitive impairment in survivors of critical illness.[257] Acute kidney injury commonly co-occurs with ARDS, complicates its management by limiting physiologic tolerance for respiratory acidosis, and is associated with worse clinical outcomes,[258 259] but acute kidney injury can be under-recognized in ARDS as a result of fluid management strategies.[260] The relation between lung injury and kidney injury is complex. Experimental models have shown that lung injury increases inflammatory mediators in the kidney independent of systemic inflammation and that renal ischemia induces pulmonary injury with impairments in fatty acid oxidation via mitochondrial damage associated molecular patterns.[261 262] Thus renal and pulmonary injury likely co-occur as a result of true organ cross-talk. Cardiac dysfunction including right ventricular dysfunction because of hypoxic vasoconstriction and global myocardial damage as a result of hypoxemia is also an important complication of ARDS.[263]

Many studies in ARDS focus on short term outcomes such as 30 day mortality and length of stay in ICU, but critical illness is a major life event with long term implications. This has increasingly come to the forefront during the covid-19 pandemic with the widely publicized syndrome of "long covid." Before covid-19, the long term effects of ARDS were already being studied.[264] ARDS can lead to pulmonary fibrosis; pulmonary function tests indicate that mild restriction with mild-to-moderate diffusion capacity abnormalities persists at one year.[265] Extrapulmonary manifestations are also common after ARDS, with persistent exercise capacity and functional limitations and psychological sequelae in both patients and caregivers up to five years after diagnosis.[266] Interestingly, although long term functional disability is common in both covid-19 and non-covid ARDS, a study comparing survivors of covid-19 ARDS with historical controls found that these limitations are more common and more severe in patients with non-covid ARDS.[267] A better understanding of the long term consequences of ARDS, their mechanisms, and interventions to improve quality of life in survivors is an important area for future study.

Emerging treatments

Mesenchymal stromal cells and extracellular vesicles

Repurposed drugs hold promise in ARDS, but novel cell based therapies including mesenchymal stromal cells (MSCs) and extracellular vesicles are also of interest. These pluripotent progenitor cells and their cellular cargo have multiple beneficial effects including promoting macrophage and T cell polarization to pro-resolving phenotypes, promoting endothelial barrier integrity, and enhancing alveolar fluid and pathogen clearance.[268]

The clinical application of MSCs and MSC derived extracellular vesicles is difficult because of differences in preparation leading to differences in viability and no standard dosing; donor-to-donor variability may also exist. A recent meta-analysis including studies of both non-covid (n=2) and covid (n=11) related ARDS concluded that MSCs are safe and reduce mortality in ARDS, but the dose and source (for example, umbilical versus bone marrow derived) of the cells differed across studies.[269] A study of alveolar biomarkers suggested a biologic benefit of MSCs with a reduction in bronchoalveolar lavage total protein, interleukin 6, soluble tumor necrosis factor receptor-1, and angiopoietin-2 in patients who received MSCs compared with placebo.[165] Multipotent adult progenitor cells, which are biologically similar to MSCs, in patients with moderate-to-severe non-covid ARDS decreased inflammatory plasma biomarkers and had a mortality benefit.[270] MSCs and extracellular vesicles have shown a trend toward benefit in studies of moderate-to-severe covid-19.[271 272] MSCs and MSC derived extracellular vesicles are an important area of future study in ARDS .

Biologic therapies

MSCs are thought to provide pleiotropic benefits in ARDS. Some other potential emerging therapies in ARDS include more targeted biologic therapies.[273] Anti-interleukin 6 therapy is likely beneficial in covid-19 when co-administered with

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corticosteroids.[274] Its use in other causes of ARDS requires further study. Anakinra, an interleukin 1 receptor antagonist, has been studied in the context of sepsis and might provide benefit for patients with sepsis and features of macrophage activation syndrome.[275] Elevated serum ferritin is a characteristic of macrophage activation syndrome,[276] and it has recently been associated with adverse outcomes including mortality in ARDS.[277] Prospective measurement of serum ferritin, transaminases, and/or triglycerides to identify patients with ARDS with characteristics of macrophage activation syndrome could be a way to enrich for a population that might benefit from interleukin 1 blockade in future studies.

Potential therapeutic targets

Other non-immune markers of tissue injury, such as angiopoietin-2, a marker of endothelial injury, and the receptor for advanced glycation end products (RAGE), a marker of alveolar type I cell injury, are possible therapeutic targets in ARDS. Elevated circulating concentrations of angiopoietin-2 and RAGE are associated with adverse outcomes in ARDS,[278 279] and they have been shown to be causally associated with its incidence in some populations.[280 281] Their pathogenic relevance make RAGE and angiopoietin-2 potentially promising targetable mediators of lung injury,[282-284] although the limited clinical data do not yet support this strategy.[285]

Challenges of clinical trial enrollment

A challenge for identifying effective drug targets in ARDS is the heterogeneity of the syndrome. For example, some patients have rapidly resolving ARDS and should probably not be included in clinical trials.[286] Overall negative results of a clinical trial might mask effects in subgroups of patients who truly benefit or experience harm. A potential strategy for enriching clinical trials is to target biologic phenotypes,[170] but this strategy is limited by a lack of readily available real time biomarker assays.[287] The European Respiratory Society recently launched the precision medicine adaptive network platform trial in hypoxemic acute respiratory failure (PANTHER), an international effort to classify clinical trial participants into biologic phenotypes in real time by using rapid biomarker platforms. This and similar efforts, including adaptive platform trials,[288] could identify new therapies for ARDS or patient subtypes for whom previously tested therapies are effective.

Guidelines

The ATS and ESICM have recently released separate updated practice guidelines (updated from their joint guidelines in 2017)[289] for the management of ARDS.[209 210] Both organizations recommend the use

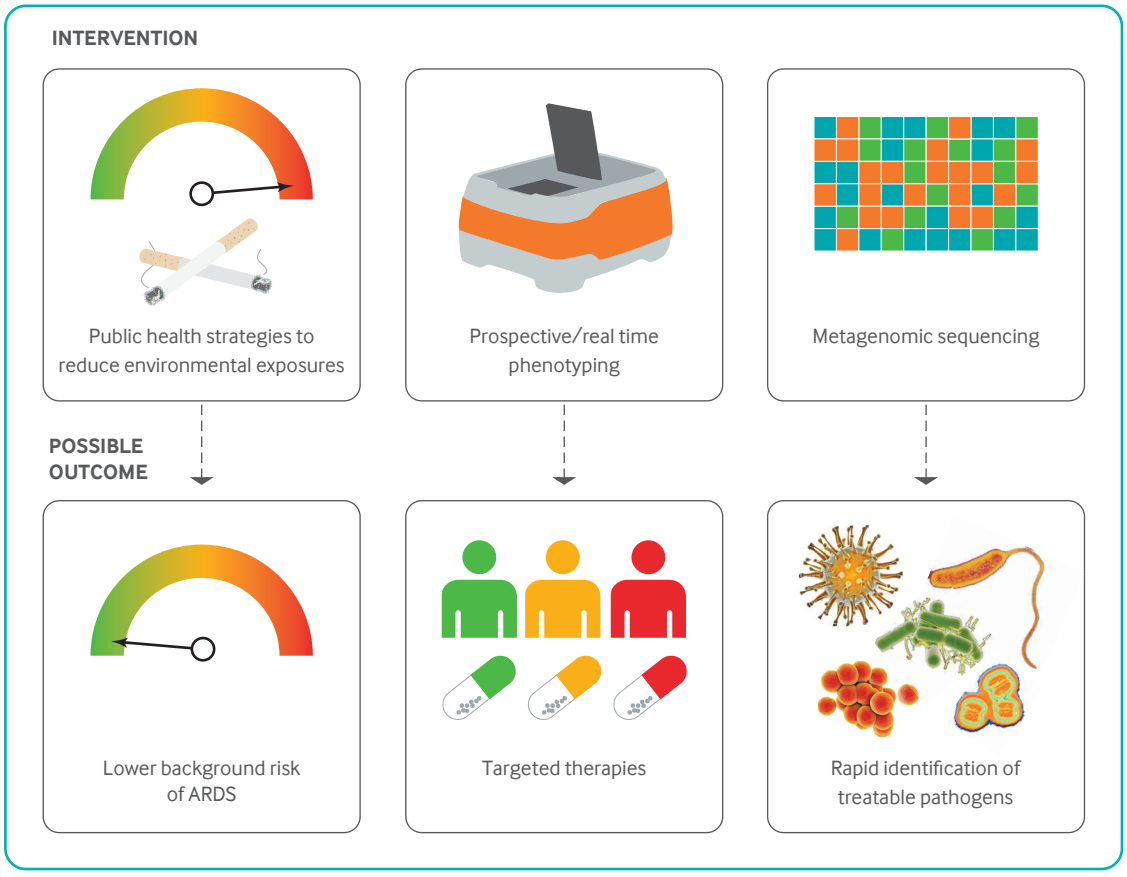

Fig 4 | Investigational interventions to improve outcomes of acute respiratory distress syndrome (ARDS)

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of low tidal volume ventilation (4-8 mL/kg predicted body weight), and the ATS also recommends limiting plateau pressure to 30 cm H_2O or less.[209 210] The guidelines also agree on a recommendation against the use of prolonged high PEEP recruitment maneuvers, and ESICM suggests against brief recruitment maneuvers as well.[209 210] Other areas of agreement are the use of prone positioning in moderate-to-severe ARDS and the use of veno-venous ECMO for severe ARDS.[209 210] ESICM also suggests awake prone positioning for non-intubated patients with covid-19 AHRF.[210]

Neither organization explicitly endorses the expanded global definition of ARDS, rather acknowledging that the evolution of the definition of ARDS is an ongoing area of discussion, although the new global definition of ARDS included substantial global input from critical care members from 21 critical care societies.[8] The ESICM guidelines discuss PICO ("patient/population, intervention, comparison, outcome") questions "applicable to ARDS being managed with HFNO," indicating that at least some patients managed with HFNO have the same disease process as those with Berlin defined ARDS.[210] The ESICM guidelines discuss the ventilatory management of non-intubated patients with ARDS/AHRF. ESICM recommends the use of HFNO over conventional oxygen therapy to reduce the risk of intubation in this population and suggests that CPAP/NIV should be used rather than COT and can be considered instead of HFNO to reduce the rate of intubation in AHRF from covid-19. The ATS guidelines do not cover this population.[209]

Key differences between the guidelines include conditional recommendations from the ATS in favor of corticosteroids in all ARDS, a high PEEP titration strategy in moderate-to-severe ARDS, and the early use of neuromuscular blockade in severe ARDS.[209] By contrast, ESICM does not cover corticosteroid use, does not make a recommendation for or against a high PEEP titration strategy, and recommends against the routine use of neuromuscular blockade in non-covid ARDS but does not recommend for or against neuromuscular blockade in covid ARDS.[210] ESICM also recommends against extracorporeal carbon dioxide removal, which is not covered by the ATS guidelines.[209 210] The SCCM has also recently released guidance specifically on the use of corticosteroids in ARDS, pneumonia, and sepsis and suggests their use in ARDS.[239]

Conclusions

ARDS is a critical illness syndrome with high morbidity and mortality, and effective therapies beyond existing strategies for supportive care are urgently needed. The covid-19 pandemic afforded many opportunities to advance our understanding of ARDS attributable to a single risk factor, but despite insights gained from this time many challenges remain. Investigation of ARDS is a rapidly developing field with many opportunities for improving the understanding of its global impact as well as its underlying biologic mechanisms, in addition to newer methods for identifying the pathogen(s) responsible for ARDS (fig 4). With the expanded global definition of ARDS, more opportunities exist to study the early pathogenesis of lung injury and the mechanisms of its progression. Early identification of patients with the new global definition of ARDS before intubation might also allow some therapies to be effective that were ineffective in trials of ventilated patients with ARDS. Global efforts to reduce the burden of critical illness will also be advanced. Several ongoing efforts are tackling the challenge of clinical and biologic

GLOSSARY OF ABBREVIATIONS

- AECC—American-European Consensus Conference
- AHRF—acute hypoxemic respiratory failure
- ARDS—acute respiratory distress syndrome
- ATS—American Thoracic Society
- CAP—community acquired pneumonia
- COT—conventional oxygen therapy
- CPAP—continuous positive airway pressure
- DAD—diffuse alveolar damage
- ECMO—extracorporeal membrane oxygenation
- ESICM—European Society of Intensive Care Medicine
- FiO_2—fraction of inspired oxygen
- HFNO—high flow nasal oxygen
- ICU—intensive care unit
- MSC—mesenchymal stromal cell
- NIV—non-invasive ventilation
- PaO_2—partial pressure of oxygen
- RAGE—receptor for advanced glycation end products
- PEEP—positive end expiratory pressure
- RCT—randomized controlled trial
- SCCM—Society for Critical Care Medicine
- TRALI—transfusion related acute lung injury

QUESTIONS FOR FUTURE RESEARCH

- How will the expanded global definition of acute respiratory distress syndrome (ARDS) affect the epidemiology and natural history of ARDS and clinical trial design?
- What is the optimum timing and duration of non-invasive respiratory support?
- What is the optimum timing and duration of mechanical ventilation via an endotracheal tube?
- Is a personalized ventilator management strategy that improves ARDS outcomes possible?
- Does a better way to categorize severity of ARDS than the PaO_2/FiO_2 ratio exist?
- Can hyper-inflammatory and hypo-inflammatory phenotypes of ARDS be prospectively validated?
- Can point-of-care biomarker platforms help to identify treatable traits and differential responses to novel and repurposed existing therapies?
- Should corticosteroids be routinely used in non-covid related ARDS?
- What is the role of cell based therapies in ARDS?
- Can we better understand the long term functional outcomes of survivors of ARDS?

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HOW PATIENTS WERE INVOLVED IN CREATION OF THIS ARTICLE

Eileen Rubin, who is a survivor of acute respiratory distress syndrome (ARDS), reviewed this manuscript. ER specifically drew our attention to the minimal change in therapies for ARDS since her diagnosis 30 years ago and the need for new clinical trial designs to individualize treatments. She also emphasized how covid-19 drew attention to racial disparities in medical care not only for chronic conditions but also for acute conditions such as ARDS.

heterogeneity, including the PANTHER platform as described above and a National Institutes of Health National Heart Lung and Blood Institute consortium to improve biologic phenotyping of patients with ARDS, pneumonia, and sepsis (APS consortium). Not only plasma but also airspace samples from patients will help to elucidate the biologic underpinning of these syndromes, including identification of new potential targets for drug therapies. This consortium will also further investigate the long term health consequences of ARDS, pneumonia, and sepsis.

Another major area of potential progress is better identification of the pathogens responsible for ARDS, especially as the microbial cause of sepsis and pneumonia is not identified in 30-60% of cases.[290] Metagenomics is a rapidly developing approach to identifying pathogens that could facilitate better understanding of treatable phenotypes and specific pathogens.[291 292] In addition, better understanding of the molecular and cellular mechanisms of lung injury is needed. New approaches that use alveolar cell biology, single cell genomics, and spatial transcriptomics in ex vivo perfused human lungs injured with live bacteria may identify new therapeutic targets.[293-298] These basic science investigations, along with further study of the global epidemiology of ARDS and phenotyping efforts for identifying targetable traits, offer the opportunity to greatly advance the understanding of ARDS in the coming years.

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